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10/564,368	01/12/2006	Atsushi Yamagishi	284112US0PCT	7782
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OBLOON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, L.L.P. 1940 DUKE STREET ALEXANDRIA, VA 22314			EXAMINER	
			SUTTON, DARRYL C	
ART UNIT		PAPER NUMBER		
1612				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/564,368	Applicant(s) YAMAGISHI ET AL.
	Examiner DARRYL C. SUTTON	Art Unit 1612

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 25 January 2010.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 2,3 and 5-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 2,3 and 5-29 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO/GS-68)
 Paper No(s)/Mail Date _____
- 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date _____
- 5) Notice of Informal Patent Application
 6) Other: _____

DETAILED ACTION

This Office Action is in response to the amendment filed 01/25/2010. No new claims have been added.

Applicant's arguments filed 01/25/2010 have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 2, 3, 5-7, 9, 12, 13 and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ubsen et al. (US 5,605,675) in view of Tomlinson et al. (4,048,300).

Ubsen et al. teach applying to the teeth a composition in two phases which do not react with one another until introduced into the oral cavity to remineralize teeth without demineralization of dental enamel (Abstract and column 2, line 66 - column 3, line 3). One phase of the composition, such as a paste, gel or solution, contains at least one water-soluble calcium salt and the other phase, i.e. paste, gel or solution, contains at least one water-soluble inorganic phosphate salt and at least one water-soluble fluoride salt, i.e. more than one fluorine source in the composition and at least one in the phase with the phosphate; in this way the ions which effect remineralization can be absorbed by the dental enamel and their subsequent reaction causes rehardening of demineralized areas in the dental enamel (column 3, lines 3-9, line 60 and line 64, column 8, lines 49-57), i.e. the calcium, phosphate and fluorine ions react to form calcium phosphate precipitate. The present invention lies in the discovery that dental enamel may be remineralized by the application of certain soluble salts yielding ions which will react to form a desirable remineralized precipitate; the anions diffuse through the tooth surface to the demineralized subsurface with the cations and form a precipitate which is bound to the tooth structure. As a result, the tooth's subsurface is remineralized when an effective amount of the two parts is utilized (column 3, lines 55-58 and line 66 – column 4, line 3). Excess salt can be present in the phases (column 4, lines 11-13). Due to the presence of the fluoride ion, the remineralized enamel is more resistant to demineralization than was the original enamel (column 4, lines 20-22). Each solution should have a pH of from about 4.5 to 10 before and after the precipitation reaction (column 4, lines 43-46). Suitable water-soluble calcium salts

include calcium glycerophosphate (column 5, lines 10-12). Calcium glycerophosphate has the anti-caries property of increasing calcium and phosphate levels in plaque.¹ Suitable water-soluble inorganic phosphates include alkali and ammonium salts of orthophosphoric acid (column 5, lines 21-26). Suitable fluoride compounds include sodium fluoride and sodium monofluorophosphate; if monofluorophosphate salts are used as the fluoride source, they could be present in the first component along with the calcium cations without departing from the present invention (column 5, lines 41-42 and lines 51-59). Completely aqueous solutions are preferred (column 9, lines 6-7). The essence of the present invention lies in the mixing of components and the quick and timely application of the resulting solution which will precipitate calcium phosphate, calcium fluoride, and calcium fluoroapatite in subsurface enamel of teeth. Before such precipitation occurs, the mixture comprising the solution must be quickly applied to the teeth (column 9, lines 33-40).

Ubsen et al. do not teach the method of alternately applying the separate compositions; the molar ratios or amounts of compounds as in instant claims 6 and 26-29; or the pH of each phase.

Tomlinson et al. teach dental preparations, such as toothpastes, tooth powders, gels and mouth washes, having calcium and phosphate components (Abstract, column 10, lines 28-30, column 18, lines 40-41). The novel compounds of the invention can be used in oral preparations and provide a long-term source of components for the remineralization of dental enamel (column 6, lines 52-58). Tomlinson teaches a

¹ Forward, G.C., Non-fluoride anticaries agents, page 209.

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composition with a first component comprised of fluoride and orthophosphoric acid with a pH of about 3 to 4; and a second component comprised of comprised of a calcium salt having a pH of about 7 (column 9, lines 28-39). Tomlinson teaches a method of alternately applying the compositions to the teeth. The teeth are subjected to fluctuating pH in the presence of fluoride, orthophosphate, and calcium ions which not only serves to prevent loss of calcium and orthophosphate ions from dental enamel, but also facilitates growth and development of the apatite crystals so that some remineralization of pits and fissures in the tooth enamel occurs. Optimum incorporation of fluoride ions into the apatite crystals structure occurs as the pH range rises from about 4 to about 7 (column 8, lines 47-68, column 17, Example 12). Apatite material containing fluoride containing materials serves to provide anti-caries protection and remineralization (column 10, lines 39-44). When orthophosphoric acid is used, an additional source of calcium ions is required such as from calcium carbonate (column 5, lines 24-27).

Tomlinson does not teach the embodiment comprised of the specific two components of the composition; or the molar ratios or amounts of compounds as claimed in claims 2-7, 9, 12, 13 and 26-29.

At the time of the invention, it would have been obvious to include the monofluorophosphate salt in the component with the calcium ions, along with incorporation of an inorganic fluoride salt, i.e. sodium fluoride, in the first component since Ubsen et al. teaches such incorporation of monofluorophosphate salt and that the composition is comprised of at least one fluoride salt. Further, it would provide

additional fluoride ions for diffusion through the dental enamel and incorporation into the calcium phosphate precipitate, helping to create remineralized dental enamel that is resistant to demineralization.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the method of Ubsen et al. to the method of alternately applying the separate compositions to teeth at the specific pHs of Tomlinson et al. motivated by the desire to facilitate the remineralization and anti-caries protection of pits and fissures in tooth enamel by simultaneously producing the optimum incorporation of fluoride ions as taught by Tomlinson et al. Further, it would negate the necessity to quickly mix and apply the composition as taught by Ubsen et al., thereby facilitating the dissolution and precipitation inside of the dentin of teeth.

In regards to claims 6, and 26-29, the prior art does not teach the specific concentrations or molar ratios of the compounds. However, the invention suggested by combining Ubsen et al. and Tomlinson et al. is comprised of from about 0.05% to 15% of a phosphate salt, from about 0.05% to 15% of a calcium salt and fluoride salt form about 0.01 to about 5%, other ingredients of the composition are optional, i.e. "may" be used, therefore, optimization of remineralization and optimization of the incorporation of fluoride in apatite crystals is obtained through routine experimentation by varying the amounts of the phosphate salt, fluoride salt, and calcium salt in the respective aqueous solvents or carriers and optionally adding and varying the amounts of other ingredients; and would result in the concentrations and molar ratios of the instant claims.

Claims 14-17 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ubsen et al. and Tomlinson et al. as applied to claims 2, 3, 5-7, 9, 12, 13 and 26-29 above, and further in view of Grabenstetter et al. (U.S. 4,083,955).

Ubsen et al. is discussed *supra*.

Ubsen et al. does not teach the times required for application of each component.

Tomlinson et al. is discussed *supra*.

Tomlinson et al. does not teach the times ranges for application of each component is from 5 to 30 seconds.

Grabenstetter et al. teach two compositions comprised of a cation, i.e. calcium, and an anion, i.e. phosphate which are sequentially applied to dental enamel resulting in mineralization of dental enamel (Abstract). The sequential application consists of two steps which may be performed in any order (column 2, lines 13-20). While the length of contact is not critical, it is necessary for the length of time to be great enough to allow diffusion of the ions through the tooth's surface (column 2, lines 51-56). The components can be sequentially delivered to the surface of the tooth by means of two separate delivery vehicles, each containing one component. The ionic ingredients can be topically applied by means of tape or other adhesive material (column 5, lines 23-27). Examples of two vehicle systems are mouthwash-mouthwash, toothpaste-toothpaste, toothpaste-mouthwash; and so forth.

Grabenstetter et al. do not teach the composition of claim 9.

In regards to claims 14-17, where the general conditions of a claim are disclosed in the prior art, it is not inventive to determine the optimum or workable ranges through routine experimentation. Therefore, the remineralization of teeth can be optimized through routine experimentation by varying amount of each component applied to the teeth and the amount of time each component is applied to the teeth; and by varying the amount of repetitions of the method.

In regards to claim 21, it would have been obvious to modify the delivery vehicle of each component since it is well known in the art that combinations of different delivery vehicles has been used to facilitate tooth remineralization.

Claims 8, 10, 11 and 18-20 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ubsen et al., Tomlinson et al. and Grabenstetter et al. as applied to claims 14-17 and 21 above, and further in view of Wiesel (U.S. Patent 6,287,120).

Ubsen et al. is discussed *supra*.

Ubsen et al. do not teach a carrier selected from paper, cloth, nonwoven fabric, absorbent cotton, sponge or porous film.

Tomlinson et al. is discussed *supra*.

Tomlinson et al. do not teach a carrier selected from paper, cloth, nonwoven fabric, absorbent cotton, sponge or porous film.

Grabenstetter et al. is discussed *supra*.

Grabenstetter et al. does not teach a carrier selected from paper, cloth, nonwoven fabric, absorbent cotton, sponge or porous film.

Wiesel teaches an embodiment of a carrier coated with a paste, gel or solution which contains medicaments which promote the repair or remineralization of tooth enamel (Abstract, column 8, lines 28-36). Wiesel teaches that the carrier is a non-woven, porous material which is first dipped in one solution and that additional solution may be applied to the porous material while it remains on the patient's teeth (column 3, lines 65-67, column 4, lines 1-5).

Wiesel does not teach a composition comprised of two components.

At the time of the invention it would have been obvious to modify the product and method suggested by combining Ubsen et al., Tomlinson et al. and Grabenstetter et al. to include the carrier of Wiesel since the method of applying compositions for remineralization of teeth with a carrier was known in the art.

In regards to claim 11, it would have been obvious to impregnate the carrier with water immediately prior to application to a tooth motivated by the desire to mix either composition with water to produce either phosphate or calcium ions immediately before applying the device to teeth.

In regards to claim 20, at the time of the invention it would have been obvious to modify the product suggested by combining Ubsen et al., Tomlinson et al., Grabenstetter et al. and Wiesel to be comprised of a mouthwash and dentifrice since the components for remineralizing teeth can be applied in different delivery vehicles as taught by Grabenstetter et al.

In regards to claims 22-25, the prior art does not teach the specific concentrations or molar ratios of the compounds. However, the invention suggested by combining Ubsen et al., Tomlinson et al., Grabenstetter et al. and Weisel et al. is comprised of from about 0.05% to 15% of a phosphate salt, from about 0.05% to 15% of a calcium salt and fluoride salt form about 0.01 to about 5%, other ingredients of the composition are optional, i.e. "may" be used, therefore, optimization of remineralization and optimization of incorporation of fluoride in apatite crystals is obtained through routine experimentation by varying the amounts of the phosphate salt, fluoride salt, and calcium salt in the respective aqueous solvents or carriers and optionally including and varying the amounts of other ingredients and would result in the concentrations and molar ratios of the instant claims.

Response to Affidavit

Applicant has submitted an affidavit to support allegations of surprise and unexpected results.

Applicant argues Winston does not disclose any Example in which Part A contains both monofluorophosphate and calcium components. The monofluorophosphate is added to Part A containing the calcium component to thereby immediately precipitate calcium phosphate. It is clear from Comparative Example B2 that adding monofluorophosphate to Part A, is not effective for fluorine uptake. Applicant argues that the skilled artisan would not expect to attain excellent fluorine

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uptake based on Winston et al., since winston is silent about claimed compositions and alternately applying them.

The Examiner disagrees.

As cited in the Non-final office action dated, 07/23/2009, and Winston et al. clearly teach the inclusion of at least one, i.e. more than one, fluoride source in the compositions and that the monofluorophosphate salt can be added to the first phase along with the calcium cations, see page 3. Comparative Example B2 discloses approximately a 10% increase in fluorine uptake as a result of the inclusion of monofluorophosphate to Part A, i.e. from 0.75 to 0.82 $\mu\text{g}/\text{cm}^2$. At the time of the invention, it was known in the art that alternately applying a two part composition comprised of a first component comprising a fluoride and orthophosphoric acid with a pH of 3 to 4 and a second component comprising a calcium salt of pH about 7 facilitates growth and development of apatite crystals and remineralization of tooth enamel; and that optimum incorporation of fluoride ions into apatite crystal structure occurs as the pH rises from about 4 to about 7, see Non-final office action dated, 07/23/2009. Accordingly, one of ordinary skill in the art would reasonably expect that fluorine uptake would be improved by alternately applying compositions comprised of fluoride and phosphate at pH of about 3 to 4 and a composition calcium containing component at pH of about 7.

Applicant argues that none of the references disclose that when monofluorophosphate is contained in the composition, fluorine uptake can be attained only by alternately applying the compositions.

As discussed *supra*. Thomlinson clearly teaches that fluorine uptake can be optimized by alternately applying a first component comprising a fluoride at pH of about 3 to 4 and a second component comprising a calcium compound at a pH of about 7.

Applicant argues that the error in the treatment of the first affidavit makes an attempt to disregard evidence of record as being irrelevant and not representing a fair comparison due to the Applicant's absence of pH data of the components used in the affidavit. Applicants disagree with the Examiner's new allegations concerning the importance of fluctuating pH in dual component compositions for remineralization of teeth. And submit a second affidavit that does include the pH of the individual components.

As cited *supra*. At the time of the invention, the relationship between optimum fluorine uptake and fluctuating pH was known in the art. Accordingly, pH information is relevant when considering whether alternative application of components of a composition provides surprising results in the fluorine uptake.

Applicant argues that Winston et al. disclose a product which includes a cationic part containing calcium supplier and an anionic part containing sodium fluoride and MFP, while the reference does not specifically disclose as product including fluorine in both parts or a product including both MFP and calcium salt in one part, but rather discloses that such a product would not be desirable and/or would be expected to have poor fluorine uptake.

The Examiner disagrees.

As discussed *supra*, Winston et al. teaches that more than one fluorine source can be in the composition; and that if MFP is used it can be placed in the phase with the calcium. Nowhere, does Winston teach that a composition with MFP along with the calcium would have poor fluorine uptake properties. Winston teaches that there is a "potential" loss of fluorine when combining MFP and calcium, which provides adequate motivation for incorporating another fluorine source, such as sodium fluoride in the other phase. Fluorine uptake would reasonably be expected to be optimized by alternating the components from pH of from about 3 to 4 and about 7, and would not be surprising.

Applicant directs the Examiner to Table 1 of the second affidavit which is the same data presented in the first affidavit but including pH information on the phases of the compositions for support for the allegation of surprise results.

The Table is not persuasive since, as can be seen by the pH data, the pH of the components of Comparative Example B2, hereafter, B2, is the same, i.e. 5.5, whereas component A of the Example has a pH of 8.1 and that of component B is about 4. Based on what was known in the art about optimum fluorine uptake and fluctuating pH, it is not surprising that the Example exhibited increased uptake over B2. As cited above, the addition of MFP to phase A of B2, i.e. increase fluorine ion availability, increased the uptake approximately 10%, even with the lack of pH fluctuation. The substitution of calcium nitrate with calcium glycerophosphate in Comparative Example B3, hereafter B3, reveals one method of adjusting the pH of the composition. Accordingly, B3 would be expected to provide increased fluorine uptake over B2 when phases A and B are alternately applied. However, Applicant has decreased the amount

of fluorine available by removing sodium fluoride from phase B. Accordingly, it would reasonably be expected that B3 would provide poorer fluorine uptake. As cited *supra*, Winston et al. teaches that at least one, i.e. more than one, fluorine source, and Applicant's composition B3 includes MFP in phase A and sodium fluorine in phase B. Based on availability of fluorine ions and knowledge of the connection between fluctuating the pH and optimum fluorine uptake the results of Table 1 are not surprising.

Applicant directs the Examiner to Table 3 to support allegations of surprise results.

The Table and argument are found unpersuasive for the reasons of record, cited in the Final office action dated 10/31/2008, see pages 9-12.

Applicant directs the Examiner to Table 4 to support the allegations of surprise results. The fluorine uptake amount of Comparative Examples C1 and C2, hereafter C1₄ and C2₄, could be increased since the pH of each is very low. However, the HAP pellets were melted because of their low pH.

This is found unpersuasive. The pH of the phases of C1₄ and C2₄ are relatively the same as Applicant's Example. Accordingly, the effect of the pH on the HAP pellet would be expected to be the same. The adjustment to the pH and subsequent alternative application of the phases has increased fluorine uptake as would be expected based on the disclosure of Thomlinson. As discussed *supra*, the substitution of calcium nitrate with an equivalent calcium source, i.e. calcium glycerophosphate, is a method of adjusting the pH of the composition versus adding sodium hydroxide. Accordingly, one would reasonably expect C2₄ to exhibit increase fluorine uptake, but as

above, Applicant has removed a source of fluorine from the composition which would reasonably be expected to result in a decrease in fluorine uptake, since there is less available fluorine than the other examples.

Applicant directs the Examiner to Table 5 and Figure 1 and argues that since the HAP pellets were melted, the buffering capacity of the mixed compositions A and B was investigated. The mixed solution of C₁₄ and C₂₄ has low pH because of the buffering capacity of the calcium salts included therein, i.e. calcium nitrate, and therefore teeth would not be repaired, but melted. C₁₄ and C₂₄ do not increase production of a salt of calcium phosphate and to increase fluorine uptake.

This is found to be unpersuasive. As cited *supra*, the pH of the phases of the composition and fluorine availability are crucial to remineralization of enamel. Accordingly, it would have been obvious to substitute calcium nitrate which produces a phase with a pH outside of the amount taught to be useful by Thomlinson, i.e. 5.5 versus about 7, with calcium glycerophosphate and expect that alternating the phases of the composition to fluctuate the pH would result in increased fluorine uptake in calcium phosphate precipitates.

All claims are rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Darryl C. Sutton whose telephone number is (571)270-3286. The examiner can normally be reached on M-Th from 7:30AM to 5:00PM EST or on Fr from 7:30AM to 4:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass, can be reached at (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Darryl C Sutton/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612